Remarks/Arguments

The foregoing amendments are fully supported by the specification as originally filed, and do not add new matter. Specific support for a library of non-oligomeric organic compounds is at least at page 2, lines 1-5; page 3, lines 25-28; the passage bridging pages 16 and 17; and the passage bridging pages 18 and 19. The latter passage provides support also for the recitation of at least 2, at lest 25, and at least 100 library members in newly added claims 83, 84 and 85, respectively. Support for the recitation of the "greatest relative affinity" for a target protein and the "most abundant" target protein-compound conjugate is, for example, at page 15, line 19 through page 16, line 3.

Turning to the final Office Action mailed on July 10, 2003 (Paper No. 13), prior to the present amendment claims 58, 59, and 61-66 were pending in this application. Claims 62-64 and 66 have been withdrawn from consideration as a result of a restriction requirement; the remaining claims were rejected on various grounds.

Claim Rejections - 35 U.S.C. §112, first paragraph

Claims 58-61 and 65 were indicated as being rejected under 35 U.S.C. §112, first paragraph for alleged lack of adequate written description. Since claim 60 was canceled in Paper No. 10, it is erroneously included in this rejection. The rejection of the remaining claims is respectfully traversed.

Summary of the Examiner's Position

According to the rejection, the scope of claim 58 "includes an infinite number of methods for identifying an 'infinite' number of possible ligands that would bind to an 'infinite' number of potential sites on an 'infinite' number of proteins that have not been 'specifically' disclosed by Applicants." The Examiner adds that the specification and claims "do not provide ***any*** guidance as to where these "sites of interest" might reside on these undisclosed target proteins," and notes that "Applicants have disclosed only ONE example . . . which would not teach a genus that

would encompass virtually an unlimited number of proteins, ligands (in a broad range of classes, i.e., both inorganic and organic) and linkers." (Emphasis original.) From this, the Examiner concludes that "one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe this enormous genus," and therefore "applicants were not in possession of the claimed genus."

Addressing Applicants' arguments in traversing a similar rejection from the prior Office Action mailed February 20, 2003, the Examiner repeats that Applicants must set forth a representative number of examples that would allow a person of skill in the art to determine that Applicants were in the possession of the invention within the full scope of claims, and maintains that the CAFC's holding in *University of California v. Eli Lilly* is applicable to the present situation and supports the Examiner's position. In further support of the rejection, the Examiner cites Delano, *Current Opinion in Structural Biology* 2--2, 12, 14-20, but notes that the citation of this reference has not been legally necessary, since Applicants' disclosure of only one working example is not representative of the broad scope of claims. Finally, the Examiner adds that "Applicants should not be afforded greater protection under the law that they are actually entitled to just because their invention is inherently difficult to adequately describe."

Applicants' Rebuttal of the Rejection

Starting with the latter remark, Applicants have not thought and are not seeking "greater protection under the law than they are actually entitled to." On the contrary, it is Applicants position that the current rejection is legally incorrect, and, if upheld, would deprive Applicants' invention of the protection to which it is legally entitled.

Secondly, the Examiner is incorrect in stating that the citation of the Delano reference was not necessary, and the reference has been cited "for the sole purpose of adhering to Applicants' request" to "provide specific scientific reasoning why one skilled in the art would not accept that at the effective filing date of the present application applicants were in the possession of the invention." It is not Applicants but the law, and its implementation in the Revised Written Description Guidelines, that mandate the Examiner to provide evidence or specific reasoning

why a skilled artisan would doubt applicants' assertion of written description thereby meeting his burden of proof.

A mere assertion that "'one working example' is not 'representative' of such broad scope" clearly does not meet the Examiner's burden of establishing a *prima facie* case of lack of adequate written description. This is particularly so, since the law does not require the presence of a representative number of "*examples*" to enable a genus. Instead, written description for a claimed genus may be satisfied through *description* of a representative number of species. Description may come in a variety of forms, including description in the specification, representation in a drawing, etc. An applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 U.S.P.Q.2D (BNA) 1961, 1966 (1997). The law is clear that it is the "*specification*" as a whole, and *not solely the working examples* that need to be examined in order to determine whether the written description provided is sufficient to support the invention as claimed. Indeed, as evidence of possession, an actual reduction to practice (such as a working example) is not always required, and what is conventional or known to one skilled in the are need not be described (Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 19USPQ2d 1111 (Fed. Cir. 1991). This is also supported by the CAFC's holding in University of California v. Eli Lilly, where the court stated:

> a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the *recitation* of the sequence of nucleotides that make up the DNA. See Fiers, 984 F.2d at 1171, 25 U.S.P.Q.2D (BNA) at 1606. A description of a genus of cDNAs may be achieved by means of a *recitation* of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a *recitation* of structural features common to the members of the genus, which features constitute a substantial portion of the genus. 119 F.3d 155; 43 U.S.P.Q.2d (BNA) 1398 (1997), emphasis added.

As detailed in Applicants' response to the prior Office Action, the specification of the present application contains a long recitation of target proteins, the sequences of which were well known in the art at the priority date of the present application (page 8, line 14 through page 9, line 12, listing a numerous classes of proteins, and over 30 specific proteins); recites a long list of chemically reactive groups (page 14, line 24 through page 16, line 23), and organic compounds by reference to their chemical structures, size, reactive groups, applicable chemistries, etc. (Page 16, line 24 through page 20, line 14.

In conclusion, the Examiner's heavy reliance on the fact that the specification contains one working example reflects improper legal analysis and is insufficient to support a conclusion that applicants were in the possession of the full scope of the claimed invention as of the effective filing date of the application.

Delano, *Current Opinion in Structural Biology* 2002, 12:14-20, was cited to illustrate "some of the challenges faced by today's researchers that are trying the analyze 'hot spots' in protein-binding interfaces (e.g. proteins that bind to other proteins and/or other ligands)." The Examiner specifically notes that Delano points at potential destabilizing perturbations that occur as a result of alanine scanning, and adds that "Applicants' claimed method requires 'mutations' in the target protein . . . that would prevent said target protein from binding to its ligand(s) just as the 'alanine mutations' interfered with the protein-protein and/or protein-ligand interactions in Delano," and that "Applicants would not be able to determine *a priori* whether their required 'mutations' would or would not destabilize."

The Examiner is incorrect in stating that the claimed method "requires" mutations in the target protein. The specification is clear in explaining that the biological target molecule, such as a target protein, is

> "chosen ***such that it possesses or modified to possess*** a chemically reactive group, which is capable of forming a covalent bond with members of a library of small organic molecules. For example, many biological target molecules naturally possess chemically reactive groups (for example, amine groups, thiol groups, aldehyde groups, ketone groups, alcohol groups and a host of other chemically

reactive groups; . . .) to which members of an organic molecule library may interact and covalently bond. In this regard, it is noted that polypeptides often have amino acids with chemically reactive side chains (e.g., cysteine, lysine, arginine, and the like)." Page 9, lines 13-22; emphasis added.

In cases where the target protein naturally contains a chemically reactive group, the Examiner's reliance on Delano is irrelevant, since there are no mutations, therefore one need not address the issue of potential destabilizing mutations.

In cases where chemically reactive groups, such as cysteines in the case of a protein, are introduced into the target molecule, such derivatization occurs prior to contacting the derivatized target molecule (protein) with a library of non-oligomeric organic compounds, in a step that is not included in the claims pending. The invention as claimed starts with the step of contacting a target protein already having a chemically reactive group (naturally or introduced by other means), with a library of small organic molecules each being capable of binding covalently to such chemically reactive group. Therefore, such derivatized target protein is merely a starting material for the invention, which can be obtained from any source, and used after it is validated that the derivatization does not significantly interfere with the target protein-small organic molecule interaction.

In further support of Applicants' position, enclosed is a Declaration of Dr. Warren L Delano, the first author of the cited paper. Dr. Delano is a founder and CEO of DeLano Scientific L.L.C., a private software company, and has a Ph.D. in Biophysics and a Bachelor of Science Degree in Molecular Biophysics and Biochemistry. Dr. Delano is, therefore, unquestionably a person skilled in the art. In paragraph 6 of his Declaration, Dr. Delano confirms that

> the claimed invention does not require mutations. If a suitable reactive group is already present, then the inventive method can be used on the wild type protein.

In paragraph 7, Dr. Delano explains that

> . . . the concept of "hot spots" is moot with respect to the vast majority of potential targets because the sited of interest are already known (e.g., active sited with respect to enzymes and ligand binding sites with respect to receptors). As described in my publication, hot spots are relevant to protein-protein and protein-

> peptide interactions. Because these interactions involve large surface areas, it was previously believed that small molecule modulators of these types of interactions may not be possible. The concept of "hot spots" was developed in part by Dr. James Wells (one of the founders of Sunesis Pharmaceuticals, Inc. and a co-inventor of the claimed invention) when he discovered that a surprisingly few residues were responsible for most of the binding interaction. As a result, a hot spot residue is defined as one that when mutated to alanine, gives rise to a distinct drop in the binding constant. In other words, if a hot spot residue in a protein were mutated to alanine, it results in a destabilizing perturbation at the protein interface such that it disrupts its interaction with its protein partner. Because protein-protein interactions appear to be modulated in large part by these hot spot residues, small molecule modulators directed at such residues could be developed to disrupt such interactions for therapeutic benefit.

In paragraph 8, Dr. Delano adds that even if the identification of such hot spots becomes necessary, despite the difficulties, such "hot spots can be and are identified."

In paragraph 9, Dr. Delano states that "the consequences of making mutations of hot spot residues are generally different from those of other residues on protein surfaces," and adds that "identifying residues for making mutants for use in the claimed invention is well within the skill of the art."

Finally, in paragraph 10 of the Declaration, Dr. Delano confirms that "the claimed invention has been useful for identifying ligands on a variety of protein targets, including those involved in protein-protein interactions."

Accordingly, the Declaration by the lead author of the cited paper establishes that the Examiner's reliance on Delano et al. does not support the conclusion that one skilled in the art would doubt that applicants were in the possession of the claimed invention at the effective filing date of the present application.

In addition, Delano's only possible relevance concerns the "sites of interest" on target proteins, and does not provide any support for the Examiner's contention that sufficient written description is not present for the genus of "ligands," "chemically reactive groups," or "target proteins." Accordingly, the Examiner is yet to provide any scientific reasoning or evidence why

one skilled in the art would not accept that Applicants knew at the effective filing date of the present application how to select chemically reactive groups, and how to provide small molecule ligands with appropriate reactivities on a wide-range of target proteins.

As further evidence that the claimed genus meets the statutory written description requirement, enclosed with the present Amendment and Response is a Declaration under 37 C.F.R. § 1.132 by Gary W. Ashley, Ph.D. Dr. Ashley, who has over twenty-five years of experience in the relevant field, has read the specification of the present application and the claims currently pending. Based on extensive disclosure in the specification concerning the chemistry of the ligands screened, the identity of representative target proteins and suitable covalent bonds, and also in view of his expertise in the field of small molecule drug screening, Dr. Ashley concluded that "the claimed screening method is generally applicable for screening a variety of small molecule ligands for a variety of target proteins, using a variety of covalent bonds, as described in the specification and as claimed in the above-identified patent application." From this, Dr. Ashley concluded that the inventors were in the possession of the invention as claimed at the time the application was filed.

In view of the foregoing arguments and declaratory evidence, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections - 35 U.S.C. § 103

(1) Claims 58-61 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Pitner et al. (U.S. Patent No. 5,367,058) and Ganem et al., *Journal of the American Chemical Society* 1991, 113(16), 6294-6.

According to the Examiner's analysis, Pitner et al. meets all limitations of claim 58, with the exception of a specific teaching of mass spectrometry analysis, which is provided by Ganem et al.

Applicants submit that the cited combination does not make obvious the invention claimed in the present application.

Claim 58, as currently amended is directed to a method of identifying a ligand less than 200 daltons in size "that has the greatest relative affinity for a target protein" by the following steps:

(a) contacting in a mixture a target protein with a library of non-oligomeric organic compounds that are each capable of binding covalently to a chemically reactive group on the target protein, thereby forming a target protein-compound conjugate;

(b) analyzing the mixture by mass spectrometry; and

(c) detecting the most abundant target protein-compound conjugate that is formed, and determining the identity of the compound present in said conjugate as the compound having the greatest relative affinity for the target protein,

wherein said compound is a novel ligand for said target protein.

Pitner et al. does not meet element (a) of claim 58, since it involves combining a known antibody-antigen pair, i.e. reacting a *single* antibody with a *single* compound, and not a *library* of compounds with a target protein.

As the Examiner has acknowledged, Pitner et al. does not meet element (b) of claim 58, since it does not teach analysis by mass spectrometry.

Pitner et al. does not meet element (c) of claim 58 either, since it does not teach the detection of the most abundant target protein-compound conjugate (indeed, it only deals with a single conjugate at any given time). In addition, Pitner et al. does not determine the identity of compound in present in such conjugate, since it concerns combining a known antibody-antigen pair, therefore, there is no need for identifying either of the binding partners.

Finally, Pitner et al. does not teach the identification of *novel* ligand of a target protein.

Ganem et al. is cited for its disclosure of mass spectrometry analysis.

Even if one assumes arguendo that the purported combination is legally proper, Ganem does not remedy the deficiencies of Pitner et al., since it fails to meet the limitations of elements (a) and (c) of claim 58.

Claim 60 has been canceled. Claims 59 and 61 depend on claim 58, carrying its recitations, and are not made obvious for the same reasons.

A similar analysis applies to newly added claim 86, and dependent claim 87. The cited combination fails to teach a competition assay including contacting in a mixture a target protein, a reducing agent, and at least two compounds, and detection of the most abundant target protein-compound conjugate formed.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(2) Claims 58-61 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Pitner et al. and Loo et al., *Mass Spectrometry Reviews*, 1997, 16, 1-23.

Pitner et al. was cited as in the previous rejection.

Loo et al. was cited for its teaching of the use of mass spectrometry for the "identification of novel protein-ligand interactions."

Pitner et al. has been discussed in response to the previous rejection. Applicants have shown that there is more difference between Pitner et al. and the invention claimed than the use of mass spectrometry. Specification, Applications have shown that Pitner et al. fails to meet limitations (a), (b) and (c) of claim 58. Loo et al. does not remedy the deficiencies of Pitner et al., since its teaching of mass spectrometry, when combined with Pitner et al., is insufficient to meet all limitations of claim 58, or the pending claims dependent on claim 58.

Similarly, newly added claims 86 and 87 should not be held obvious, since the cited combination does not teach a competition assay, involving the screening of a mixture containing at least two compounds with a target protein, as recited in claim 86.

Accordingly, the present rejection is believed to be misplaced, and should be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 58, 59, and 61 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Przybylski et al. (IDS Reference, Paper No. 11). The rejection is respectfully traversed.

Przybylski et al. discusses the use of electrospray mass spectrometry of biomacromolecular complexes with *nonvovalent* interactions. Przybylski et al. does not teach the step of contacting, in a mixture, a target protein with a library of nonoligomeric organic compounds, since its cited disclosure concerns the interaction of an individual ligand with an individual target protein. Furthermore, the interaction between the ligand and the target protein is not covalent, since the declare purpose of the work reported by Przybylski et al. is the study of noncovalent interactions. Finally, Przybylski obviously has no disclosure whatsoever of detecting the most abundant target protein-compound conjugate, since only individual and nonvovalent interactions are studied, in contrast with the invention claimed in the present application, which is a screening assay, where a library of small molecules is screened in order to identify a member that has the greatest affinity for the target protein.

Accordingly, Przybylski et al. clearly does not anticipate the claims rejected, and the present rejection should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39750-0002DV1). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: October 9, 2003

Ginger R. Dreger
Reg. No. 33, 055

HELLER EHRMAN WHITE & McAULIFFE LLP
Customer No. 25213
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 457571 v1
10/6/03 3:27 PM (39750.0002)